Introduction

Lung cancer is the most prevalent and fatal cancer in the Chinese population with the non-small cell lung cancer (NSCLC), accounting for 80–85% of all lung cancer cases and being the most significant subtype (1). NSCLC is further divided into squamous cell carcinoma, large cell...
carcinoma, adenocarcinoma and others, among which non-squamous NSCLC accounts for half of all NSCLC cases. In clinical settings, most NSCLC patients are diagnosed as locally advanced or systematically metastasized diseases; thus, curative surgery is unprocurable. Instead, the targeted therapy for patients with targetable genetic aberrations [such as epidermal growth factor receptor (EGFR)] improves the survival of advanced NSCLC patients. However, for patients lacking targetable genetic aberrations, chemotherapy remains the only option (2,3). Although chemotherapy, as first-line option, has brought certain benefits and there exists the choice of second-line therapy, the clinical outcomes for advanced NSCLC patients are barely satisfactory, especially when the patients fail the first-line therapy.

In various malignancies, angiogenesis is an essential mechanism for tumor growth, metastasis and recurrence. Among cancer therapeutic strategies, anti-angiogenesis agents, in combination with chemotherapy or not, have shown survival benefits in advanced-stage malignancies (4). Vascular epidermal growth factor receptor 2 (VEGFR2) is specifically responsible for angiogenesis functioning via regulating multiple signaling pathways (5). Therefore, VEGFR2 inhibitors including receptor-specific antibodies and small molecule drugs have been developed, and a few of them have been approved as standard treatment for advanced malignancies (4). Apatinib is a small molecular vascular epidermal growth factor (VEGF) tyrosine kinase inhibitor (TKI) that binds and targets the intracellular domain of VEGFR2. It has been used in advanced malignancy patients who fail the prior chemotherapy and other targeted therapies (6). The use of apatinib has been approved by FDA and cFDA for advanced gastric cancer, and supportive data from several randomized, double-blinded, placebo-controlled clinical trials illustrate that apatinib significantly improves progression-free survival (PFS) and overall survival (OS) with acceptable safety in patients with advanced gastric cancer including those who have failed two or more lines of chemotherapy (7,8).

As for advanced NSCLC, favorable survival outcomes are observed after treated with apatinib, and the drug-related toxicity is tolerable and controllable (9-11). Also, the combination of apatinib with cytotoxic drugs such as docetaxel has been proven effective in treating advanced NSCLC (12). In a previous multi center prospective study, apatinib plus docetaxel achieves ORR of 33.33%, DCR of 66.67% and median PFS of 2.92 months as the second or above line treatment in advanced non-squamous NSCLC (12). However, whether apatinib combining docetaxel would improve the treatment outcomes of advanced non-squamous NSCLC patients with wild-type EGFR is seldom reported, only a phase I trial shows promising safety and treatment response to apatinib plus docetaxel in 12 advanced lung adenocarcinoma patients with wild-type EGFR (13). Therefore, in this multi-center, phase II trial, we aimed to investigate the treatment response, survival profiles and treatment-related adverse events (AEs) of apatinib plus docetaxel in treating advanced non-squamous NSCLC patients with wild-type EGFR.

**Methods**

**Patients**

This single-arm, multi-center, phase II trial prospectively recruited 30 advanced non-squamous NSCLC patients with wild-type EGFR, and all eligible patients met following inclusion criteria: (I) histologically diagnosed as advanced non-squamous NSCLC (stage IIIIB or IV) with wild-type EGFR confirmed by EGFR mutation testing; (II) age ≥18 years; (III) had at least one measurable lesion defined by Response Evaluation Criteria in Solid Tumors (RECIST); (IV) disease progression after treatment with platinum-based chemotherapy regimen; (V) Eastern Cooperative Oncology Group performance status (ECOG PS) score 0 or 1; (VI) a life expectancy ≥3 months; (VII) adequate hematologic, hepatic, and renal function; (VIII) willingness to practice contraception during the trial. The key exclusion criteria included: (I) squamous carcinoma (including adenosquamous carcinoma) or small cell lung carcinoma; (II) history or newly diagnosed central nervous system metastases; (III) intratumor cavitation or necrosis; (IV) major blood vessel involvement; (V) uncontrolled hypertension; (VI) unstable angina, myocardial infarction, and class III or IV congestive heart failure as defined by the New York Heart Association (NYHA); (VII) suffered from thromboembolic events within the latest 12 months, including cerebrovascular accident, deep venous thrombosis and pulmonary thrombosis; (VIII) history of hemoptysis (more than one-half teaspoon of bright red blood per day, within the preceding 2 months); (IX) bleeding tendency or current treatment with coagulation therapy; (X) incapable of oral intake; (XI) intestinal paralysis or ileus; (XII) confirmed pregnancy or lactation period.

**Ethics statement**

This phase II trial (Chinese Clinical Trial Registry
Number: ChiCTR1800020105) was approved by the Ethics Committee of our hospital (Ethical Approval Number: 2016NZKY-014-01) and conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients signed the informed consents prior to enrollment and were voluntary to comply with treatment protocol, follow-up assessments and procedures.

**Baseline data collection**

After enrollment, patients’ baseline characteristics were documented, which included age, sex, ECOG PS score, number of metastatic sites, prior treatments (surgery, chemotherapy, radiotherapy, target therapy, first-line treatment regimen), prior lines of treatments, and PFS from first-line treatment.

**Treatment**

All patients received combined therapy of apatinib (Jiangsu Hengrui Medicine Co., Ltd, China) and docetaxel (Jiangsu Hengrui Medicine Co., Ltd, China) (Table S1). The apatinib was administered as follows: oral dose of 500 mg once daily until intolerable toxicity, disease progression, or death. A continuous 28-day treatment was defined as one treatment cycle. Dose reduction to 250 mg once daily of apatinib was allowed if patients experienced grade 3/4 hematologic AEs, or other non-hematologic AEs that the investigators considered it was necessary to reduce dose. The docetaxel was administered at dose of 60 mg/m² intravenously over 1 h, repeated every 3 weeks which was defined as one treatment cycle, and continued for 4–6 cycles. Treatment cessation criteria for this trial were: (I) subjects withdrew their informed consents; (II) disease progression confirmed by imaging examination; (III) subjects were still intolerable to the toxicity after dose adjustment; (IV) other circumstances where the researcher considered it necessary for subjects to withdraw from the trial. Besides, after trial discontinuation, apatinib plus docetaxel or combined chemotherapy was allowed for patients with disease progression at the discretion of the investigators and patients.

**Endpoints and outcome evaluation**

The primary endpoint was PFS. Secondary endpoints included OS, objective response rate (ORR) and disease control rate (DCR) at first evaluation after one-month treatment, and AEs. Since starting therapy, all patients were followed-up monthly by phone call or clinic consultation according to the scheduled protocol, and the survival status and AEs were documented, which was lasted until death, patient dropping-out or the end of the trial. The PFS was calculated from the date of initial treatment by apatinib and docetaxel to the date of disease progression or death (whichever occurred first). OS was calculated from the date of initial treatment by apatinib and docetaxel to the date of death. Treatment response was evaluated according to RECIST 1.1, which was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). ORR was defined as CR + PR, and the DCR was defined as CR + PR + SD. First tumor response assessment was performed at one-month treatment of apatinib and docetaxel by the institutions’ radiology group using enhanced computed tomographic or magnetic resonance imaging scan. AEs were assessed and graded following the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0) and classified as degree 0–4.

**Statistical analysis**

Twenty-nine patients were included in response and survival analysis, and one patient without response and survival assessments due to early lost follow-up was excluded. While all 30 patients were included in the safety analysis. Descriptive analysis was displayed as mean and standard (SD), median and interquartile range (IQR), or number and percentage [No. (%)]. PFS and OS were illustrated by Kaplan-Meier survival curves. Statistical analysis was performed using SPSS 22.0 software (IBM, USA).

**Results**

**Study flow**

Thirty NSCLC patients were eligible for enrollment, and signed the informed consents (Figure 1). All patients received apatinib plus docetaxel treatment, and 8 of them continued treatment but 22 of them discontinued due to disease progression (n=15), death (n=6), lost follow-up after 3 doses of apatinib (n=1). Finally, 29 patients were included in response and survival analysis, while 1 patient without response and survival assessment due to early lost follow-up...
was excluded; meanwhile, all 30 patients were included in the safety analysis.

**Baseline characteristics**

The enrolled NSCLC patients were aged 60.17±9.79 years in average with 19 (63.3%) being males and 11 (36.7%) being females (Table 1). There were 5 (16.7%) patients with ECOG PS score 0 and 25 (83.3%) patients with ECOG PS score 1. Number of patients with 0, 1, 2 and 3 metastatic sites was 8 (24.7%), 5 (16.7%), 13 (43.3%) and 4 (13.3%) respectively. The mean/median PFS from first-line treatment were 5.93±5.62/4.43 (1.97–6.40) months. Other clinical characteristics of NSCLC patients were shown in Table 1.

**Treatment response**

Since one patient lacked response and survival assessment due to early lost follow-up, 29 patients were included in treatment response and survival analysis. Assessment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NSCLC patients (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>60.17±9.79</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>ECOG PS score, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>1</td>
<td>25 (83.3)</td>
</tr>
<tr>
<td>Number of metastatic sites, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (24.7)</td>
</tr>
<tr>
<td>1</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>2</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>3</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Previous surgery of primary tumor, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>No</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>Previous chemotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>No</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>Previous radiotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>No</td>
<td>26 (86.7)</td>
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<td>Previous target therapy, n (%)</td>
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<tr>
<td>Yes</td>
<td>4 (13.3)</td>
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<td>No</td>
<td>26 (86.7)</td>
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<tr>
<td>Pemetrexed plus platinum-based regimen as</td>
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<tr>
<td>first line treatment, n (%)</td>
<td>30 (100.0)</td>
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<tr>
<td>Prior lines of treatments, n (%)</td>
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<tr>
<td>1</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>2</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>PFS from first-line treatment (months)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.93±5.62</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.43 (1.97–6.40)</td>
</tr>
</tbody>
</table>

Table 1: Baseline characteristics of the enrolled patients

NSCLC, non-small cell lung cancer; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; IQR, interquartile range.
of treatment response revealed that no patient achieved CR (0.0%), 8 patients achieved PR (27.6%), 20 patients were with SD (69.0%), and 1 patient were with PD (3.4%), resulting in ORR and DCR of 27.6% and 96.6%, respectively (Figure 2). Besides, tumor size was recorded at each examination and the change of tumor size compared with baseline of each patient was shown in Figure 3.

**Survival profile**

All patients were followed-up monthly by phone call or clinic consultation, and the survival status were documented. As calculated, the median PFS was 5.3 months (95% CI: 3.6–6.9 months) (Figure 4A), and the median OS was 9.6 months (95% CI: 6.33–12.9 months) (Figure 4B).

**Treatment-related AEs**

The common (defined as incidence >10.0%) non-hematologic AEs included: hypertension (66.7%), hand-foot syndrome (40.0%), proteinuria (36.7%), fatigue (33.3%), oral mucositis (20.0%), headache or swirl (20.0%), elevated transaminase (16.7%), diarrhea (13.3%), nausea (13.3%), hoarseness (13.3%) and TBIL/DBIL increased (13.3%) (Table 2). The common (defined as incidence >10.0%) hematologic AEs were leukopenia (26.7%), thrombocytopenia (23.3%) and neutropenia (16.7%) (Table 2). Notably, most of the AEs were at grade 1–2, and a minor proportion were at grade 3, while only one case was at grade 4 (neutropenia). Meanwhile, most of the AEs were tolerable.

**Discussion**

Apatinib has been approved in China as the third-line
Table 2  AEs related to the treatment

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Non-hematologic, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>2 (6.7)</td>
<td>8 (26.7)</td>
<td>10 (33.3)</td>
<td>0 (0.0)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>2 (6.7)</td>
<td>7 (23.3)</td>
<td>3 (10.0)</td>
<td>0 (0.0)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>5 (16.7)</td>
<td>4 (13.3)</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (6.7)</td>
<td>7 (23.3)</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>1 (3.3)</td>
<td>2 (6.7)</td>
<td>3 (10.0)</td>
<td>0 (0.0)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Headache or swirl</td>
<td>4 (13.3)</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Elevated transaminase</td>
<td>3 (10.0)</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (10.0)</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>1 (3.3)</td>
<td>3 (10)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (13.3)</td>
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<tr>
<td>TBIL/DBIL increased</td>
<td>2 (6.7)</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (3.3)</td>
<td>0 (0)</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1 (3.3)</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (6.7)</td>
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<tr>
<td>Cough</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Myelosuppression</td>
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<td>0 (0.0)</td>
<td>1 (3.3)</td>
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<td>ALP increased</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
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<td>Hematologic, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Leukopenia</td>
<td>4 (13.3)</td>
<td>1 (3.3)</td>
<td>3 (10.0)</td>
<td>0 (0.0)</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (10.0)</td>
<td>3 (10.0)</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
<td>7 (23.3)</td>
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<tr>
<td>Neutropenia</td>
<td>1 (3.3)</td>
<td>2 (6.7)</td>
<td>1 (3.3)</td>
<td>1 (3.3)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

AEs, adverse events; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin.

Treatment for advanced gastric cancer, and it is under clinical trials for other advanced malignancies including advanced NSCLC. For advanced NSCLC patients who fail the first or above chemotherapy/targeted therapy, the use of apatinib shows promising efficacy and manageable toxicity (14,15). In a pooled analysis of 14 studies including a total of 457 advanced NSCLC patients, the pooled median PFS is 4.77 months and the pooled median OS is 6.85 months; in addition, the pooled ORR and DCR values are 18% and 72% respectively (14). Another study reports that apatinib achieves ORR and DCR of 6.9% and 67.4%, respectively; and a median PFS as well as median OS of 3.8 months and 5.8 months respectively in 52 advanced NSCLC patients who progress after second-line or more treatments (16). In addition, in 100 stage III/IV NSCLC patients, the ORR and DCR to apatinib as third or subsequent-line therapy are 11.0% and 67.0% respectively; the median PFS is 2.93 months (15).

Docetaxel is recommended as the second-line chemotherapy for advanced NSCLC patients with wild-type EGFR (17). Previous report reveals the median PFS and OS to docetaxel as 4.2 and 9.4 months respectively in advanced non-squamous NSCLC patients (18). Despite that, the combination of anti-angiogenesis receptor TKI with docetaxel improves PFS in advanced NSCLC patients. For instance, in a phase III, double-blind and randomized-controlled clinical trial, nintedanib (anti-angiogenesis receptor TKI) in combination with docetaxel notably improves PFS and OS compared with docetaxel plus placebo in patients with previously treated NSCLC, especially in
those with adenocarcinoma (19). Additionally, combination of apatinib with chemotherapy agents, yields better treatment outcomes, including inhibiting the proliferation of NSCLC cells, reducing the micro vessel density and anti MAPK-ERK and PI3K-AKT-mTOR signaling pathway activation compared with apatinib monotherapy in NSCLC mouse xenograft model (20). These studies illustrate that there may be a synergizing effect of anti-angiogenesis receptor TKI combined with cytotoxic drugs in treating advanced NSCLC.

As for the combination of apatinib and docetaxel, the median PFS duration for this patient is 4.2 months in heavily pretreated advanced non-squamous NSCLC patients treated with apatinib plus docetaxel, which is favorable numerically referring to the previous studies (11). Furthermore, in a previous multi center prospective study, apatinib plus docetaxel achieves ORR of 33.33%, DCR of 66.67% and median PFS of 2.92 months as the second or above line treatment in advanced non-squamous NSCLC (12). Whereas for advanced non-squamous NSCLC patients with wild-type EGFR, the treatment efficacy of apatinib plus docetaxel is uninvestigated until a phase I trial shows safety and tolerability of apatinib plus docetaxel in treating a small number of advanced lung adenocarcinoma patients with wild-type EGFR. Thus, we investigated the efficacy and safety of apatinib plus docetaxel in treating advanced non-squamous NSCLC patients with wild-type EGFR in this multi-center, phase II trial. This study observed that the ORR and DCR were 27.6% and 96.6% respectively; the median PFS was 5.3 months, and the median OS was 9.6 months in advanced non-squamous NSCLC patients with wild-type EGFR treated with apatinib plus docetaxel. Numerically, the median PFS and OS were higher compared with that of apatinib or docetaxel alone in previous studies, as well as the superior rate of ORR and DCR. This might due to the synergizing effect of apatinib and docetaxel, while the detailed mechanism was not investigated in this study.

The common apatinib-related AEs include hypertension, proteinuria, hand-foot-skin reaction, fatigue, oral mucositis and hematologic toxicity. In a clinical trial using apatinib plus docetaxel, the common treatment-related AEs included hypertension (66.7%), hand-foot syndrome (40.0%), proteinuria (36.7%), fatigue (33.3%), oral mucositis (20.0%), headache or swirl (20.0%); and hematologic toxicities including leukopenia (26.7%), thrombocytopenia (23.3%) and neutropenia (16.7%). Most AEs were at grade 1–2, and there existed only 1 case of grade 4 AE which was neutropenia. Taken together, the common AEs of apatinib plus docetaxel were predictable according to the AEs of apatinib or docetaxel alone, and that the high-grade AEs were rare, indicating that apatinib plus docetaxel had reasonable and controllable safety profiles in treating advanced non-squamous NSCLC with wild-type EGFR.

As a single-arm, multi-center, phase II trial, this study observed several shortcomings. The sample size was relatively small (N=30), which might slightly reduce statistical power. In addition, since this was a single-arm trial, whether apatinib plus docetaxel was comparable to apatinib/docetaxel alone required further validation by randomized, controlled trial; and whether there existed synergizing effect of apatinib and docetaxel in treating advanced non-squamous NSCLC needed to be investigated by further studies.

In conclusion, apatinib plus docetaxel presents favorable treatment efficacy and tolerable safety in advanced non-squamous NSCLC patients with wild-type EGFR.

Acknowledgments

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**Footnote**

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at [http://dx.doi.org/10.21037/jtd.2020.03.54](http://dx.doi.org/10.21037/jtd.2020.03.54)). YS serves as the unpaid editorial board member of *Journal of Thoracic Disease* from Mar 2012 to Mar 2022. The other authors have no conflicts of interest to declare.
Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This phase II trial (Chinese Clinical Trial Registry Number: ChiCTR1800020105) was approved by the Ethics Committee of our hospital (Ethical Approval Number: 2016NZKY-014-01) and conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients signed the informed consents prior to enrollment and were voluntary to comply with treatment protocol, follow-up assessments and procedures.

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analysis in a real-world setting. Medicine (Baltimore) 2019;98:e16967.


**Table S1 Apatinib treatment overview**

<table>
<thead>
<tr>
<th>Items</th>
<th>NSCLC patients (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of apatinib treatment (days)</td>
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</tr>
<tr>
<td>Median (IQR)</td>
<td>109 (51.8–167.5)</td>
</tr>
<tr>
<td>Range</td>
<td>3.0–688.0</td>
</tr>
<tr>
<td>Initial dosage of apatinib at 500 mg/day, n (%)</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>Initial dosage of apatinib at 250 mg/day, n (%)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Mean dosage of apatinib, mean ± SD</td>
<td>475±76.28 mg/day</td>
</tr>
<tr>
<td>Dosage adjustment of apatinib due to toxicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>1 time</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>2 times</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>3 times</td>
<td>2 (6.7)</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; SD, standard deviation; IQR, interquartile range.